Original Study

The Effect of Lenalidomide on Health-Related Quality of Life in Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes: Results From the MDS-005 Study

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Abstract

Health-related quality of life (HRQoL) was evaluated among red blood cell transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes (MDS) treated with lenalidomide (n = 160) or placebo (n = 79) in the phase III MDS-005 study. Lenalidomide did not worsen HRQoL; response to lenalidomide was associated with significant HRQoL improvement. Lenalidomide represents a treatment option for patients with lower-risk non-del(5q) MDS who are ineligible for or refractory to erythropoiesis-stimulating agents.

Background: The phase III MDS-005 study compared lenalidomide versus placebo in red blood cell transfusion-dependent (RBC-TD) patients with lower-risk non-del(5q) myelodysplastic syndromes (MDS), ineligible/refractory to erythropoiesis-stimulating agents. Lenalidomide-treated patients were more likely to achieve transfusion independence (TI) $\geq$ 8 weeks (26.9% vs. 2.5%; $P < .001$) and hemoglobin increase $\geq$ 1.5 g/dL (19.4% vs. 2.5%) versus placebo. **Patients and Methods:** Patients were randomized 2:1 to oral lenalidomide 10 mg once daily or placebo once daily (both on 28-day cycles). Patients with creatinine clearance 40 to 60 mL/min were given lenalidomide 5 mg once daily. Health-related quality of life (HRQoL), a predefined secondary end point, was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 questionnaire at baseline, week 12, week 24, every 12 weeks thereafter, and at discontinuation. **Results:** At week 24, lenalidomide was associated with benefit versus placebo across all 5 preselected questionnaire scales (fatigue, dyspnea, global quality of life, physical functioning, and emotional functioning). After adjustment for baseline scores, only emotional functioning achieved significance ($P = .047$). Further improvement versus baseline was observed for patients who continued lenalidomide after week 24. In post hoc analyses, achievement of TI $\geq$ 8 weeks was associated with significant improvements across all scales ($P < .01$); an increase in hemoglobin level correlated with significant improvements in all scales at week 24, except emotional functioning ($P < .05$). **Conclusion:** Lenalidomide did not adversely affect HRQoL in RBC-TD patients with lower-risk non-del(5q) MDS and response to lenalidomide was associated with significant improvements in HRQoL.

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Introduction

Anemia is present in most patients with myelodysplastic syndromes (MDS) and contributes substantially to the clinical symptoms and burden of the disease.[1] Red blood cell (RBC) transfusions might help to alleviate the symptoms of anemia,[2] but prolonged transfusion dependence is associated with increased morbidity,[3] shorter survival,[4,5]

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higher health care costs,[6,7] and poor health-related quality of life (HRQoL).[8-10] Consequently, reducing transfusion dependence and anemia-related symptoms is the main therapeutic goal in patients with transfusion-dependent lower-risk MDS.

Lenalidomide treatment results in RBC transfusion independence (RBC-TI) in more than half of patients with lower-risk MDS and del(5q),[11,12] and corresponding improvements in HRQoL have been observed.[13,14] For patients without del(5q), erythropoiesis-stimulating agents (ESAs) are the first choice treatment for anemia, and response to ESAs has been associated with improved HRQoL.[15-18] However, treatment options after failure of ESAs are limited,[2] which frequently leaves anemic patients dependent on RBC transfusions. Recently, a phase III study (MDS-005) evaluated lenalidomide in transfusion-dependent patients with International Prognostic Scoring System (IPSS) low- or intermediate-1 risk MDS without del(5q) who were ineligible for or refractory to ESAs.[19] In this study, the proportion of patients who achieved RBC-TI $\geq$ 8 weeks was significantly higher in the lenalidomide group than in the placebo group (26.9% vs. 2.5%; $P < .001$), with most responding within 16 weeks of treatment. A higher proportion of patients in the lenalidomide group achieved a hemoglobin increase of $\geq$ 1.5 g/dL compared with the placebo group (19.4% vs. 2.5%).

Health-related quality of life was a prespecified secondary end point of the MDS-005 study.[19] This report presents detailed results of the primary and additional post hoc analyses of patient-reported outcomes data collected from the MDS-005 study to assess the effect of lenalidomide treatment on HRQoL in lower-risk non-del(5q) MDS patients.

Patients and Methods

The MDS-005 trial was a randomized, placebo-controlled, double-blind phase III study that evaluated the efficacy and safety of lenalidomide in patients with IPSS low- or intermediate-1 risk MDS without del(5q) who were ineligible for or refractory to ESA treatment. Full details of the study supporting the efficacy, safety, and selected HRQoL findings have been published previously.[19] The study was approved by individual institutional review boards of participating centers and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment. The trial was registered as NCT01029262 at *https://clinicaltrials.gov*.

Study Design

Eligible patients were aged 18 years or older, had transfusion-dependent anemia (transfusion dependence was defined as an average transfusion requirement of $\geq$ 2 units packed RBCs every 28 days and no 8 consecutive weeks without RBC transfusions in the 16 weeks before randomization) due to IPSS low- or intermediate-1 risk MDS, had non-del(5q) karyotype, and were ineligible for or refractory to ESAs (defined as: [1] RBC transfusion dependence despite ESA treatment of $\geq$ 40,000 units per week recombinant human erythropoietin or equivalent dose of darbepoetin for 8 weeks; or [2] serum erythropoietin level > 500 mU/mL in patients not previously treated with ESAs).

Patients were randomized 2:1 to oral lenalidomide 10 mg once daily or placebo once daily (both on 28-day cycles). Patients with creatinine clearance 40 to 60 mL/min were given lenalidomide 5 mg once daily. Patients with RBC-TI $\geq$ 8 weeks or erythroid response by week 24 continued double-blind treatment until erythroid relapse, disease progression, unacceptable toxicity, or consent withdrawal.

Clinical End Points

The primary clinical end point of the trial was the proportion of patients who achieved RBC-TI for $\geq$ 8 consecutive weeks. Secondary clinical end points included RBC-TI $\geq$ 24 weeks, progression to acute myeloid leukemia, overall survival, HRQoL, and safety.

Assessment of HRQoL

A schematic overview of the methodology used in the MDS-005 study for the assessment of HRQoL is presented in Supplemental Figure 1 in the online version. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (EORTC QLQ-C30)[20] at baseline, week 12, week 24, every 12 weeks thereafter, and at discontinuation. The QLQ-C30 is a well validated and commonly used questionnaire in MDS research.[21] It consists of 30 items, including 5 multi-item functional scales (physical, role, emotional, social, and cognitive), 3 multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global health status/quality of life scale, and 6 single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The standardized scores for this questionnaire range from 0 to 100, with higher scores indicating greater levels of functioning or more severe symptoms. Data were collected electronically using tablet computers. All HRQoL scales of the QLQ-C30 were analyzed; however, the analysis focused on 5 preselected and clinically relevant scales[22-25]: fatigue, dyspnea, global quality of life, physical functioning, and emotional functioning.

Statistical Analyses

Analyses of HRQoL were based on patients in the intent-to-treat (ITT) population who completed the baseline HRQoL assessment and had $\geq$ 1 postbaseline assessment available (ie, the HRQoL-evaluable ITT population). The statistical methods are described in further detail in Supplemental Appendix A in the online version.

Results

Patients

From February 2010 to June 2013, 239 patients were enrolled at 72 treatment centers and randomized to lenalidomide (n = 160) or placebo (n = 79), constituting the ITT population. Baseline characteristics were comparable between the 2 treatment groups; overall, the median age was 71 years (range, 43-87); 162 were male; median time from diagnosis was 2.6 years (range, 0.1-29.6); and 118 had an Eastern Cooperative Oncology Group score of 1 or 2. Patients had received a median of 3.0 packed RBC units per 28 days (range, 1.5-9.8), and 200 had received previous therapy, 188 of whom received ESAs. Overall, 122 of 160 (76.3%) patients in the lenalidomide group and 56 of 79 (70.9%) patients in the placebo group completed a baseline HRQoL assessment and had $\geq$ 1 follow-up assessment available, thus constituting the HRQoL-evaluable ITT population.

Table 1 Response Compliance Rates for the EORTC QLQ-C30

Scheduled Visit	Lenalidomide	Placebo	*P*
Baseline	144/160 (90.0)	70/79 (88.6)	.823
Week 12	134/160 (83.8)	62/79 (78.5)	.371
Week 24[a]	91/106 (85.8)	50/62 (80.6)	.391
Week 36	33/41 (80.5)	4/4 (100)	1.000
Week 48	23/32 (71.9)	1/2 (50.0)	.508

Data are presented as n/N (%) except where otherwise stated.
Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; RBC-TI = red blood cell transfusion independence.
[a]Only patients with RBC-TI ≥ 8 weeks or erythroid response by week 24 continued double-blind treatment.

Questionnaire Compliance

Response compliance rates for the HRQoL questionnaire were high and did not differ significantly between treatment groups across all assessment visits ($P > .05$; Table 1). Compliance rates for the combined lenalidomide and placebo groups were 89.5%, 82.0%, 83.9%, 82.2%, and 70.6% at baseline and weeks 12, 24, 36, and 48, respectively. No significant differences were seen in key baseline characteristics between compliant and noncompliant patients within each treatment group ($P > .05$; data not shown).

Health-Related Quality of Life Outcomes at Baseline and Follow-up

At baseline, mean scores for each scale of the QLQ-C30 did not differ significantly between treatment groups (see Supplemental Table 1 in the online version). Compared with HRQoL data reported for the general population,[26] baseline HRQoL scores for patients in the MDS-005 study were worse, particularly for global quality of life, physical functioning, role functioning, fatigue, dyspnea, and constipation (see Supplemental Table 1 in the online version). At week 12, mean changes in HRQoL scores from baseline were not significantly different between treatment groups across the 5 preselected HRQoL scales (Figure 1). At week 24, lenalidomide was associated with significantly less fatigue ($P = .046$) and better emotional functioning ($P = .035$) compared with placebo (Figure 1). After week 24, an improving trend was observed across all preselected scales in patients who continued treatment with lenalidomide; the number of patients in the placebo group was too small to show a trend, because most had discontinued study drug by this time point (Figure 1). No significant difference in mean change from baseline between treatment groups was observed for the remaining unselected scales, except for a significant improvement in insomnia at week 24 in the lenalidomide group compared with placebo ($P = .038$; data not shown).

After adjusting for baseline scores, changes in HRQoL from baseline were not significantly different between treatment groups at week 12 (Figure 2). At week 24, only change in emotional functioning was statistically significant (+ 0.8 with lenalidomide vs. −7.1 with placebo; $P = .047$) in the preselected scales; however, no adjustment for multiplicity was performed. In the remaining unselected scales, lenalidomide was associated with a significant improvement in insomnia ($P = .004$) and a significant worsening in diarrhea ($P = .050$) at week 24 compared with placebo (data not shown).

Differences in predicted least-squares mean changes in HRQoL scores at week 24 for the preselected scales are shown in Figure 3. Lenalidomide was associated with better HRQoL scores versus placebo across all preselected scales, particularly fatigue, dyspnea, and emotional functioning. None of the scales reached statistical significance, possibly due to small sample size. The analyses were not adjusted for the imputation of missing data; however, our analyses were consistent with results of analyses using complete cases, last observation carried forward, and pattern mixture approaches to imputing missing data.

The proportion of patients in the lenalidomide and placebo groups categorized as having clinically meaningful improvement or worsening in preselected HRQoL scales at week 24 is shown in Figure 4. For each scale, the lenalidomide group had a larger proportion of patients with clinically meaningful improvement and a smaller proportion with clinically meaningful worsening compared with placebo, although the difference between groups was not statistically significant for any of the scales.

Relationship Between Achievement of RBC-TI ≥ 8 Weeks Response and Changes in HRQoL Outcomes

In a post hoc analysis based on HRQoL-evaluable patients who completed a baseline HRQoL assessment and ≥ 1 postbaseline assessment (lenalidomide, n = 134; placebo, n = 62), achievement of RBC-TI ≥ 8 weeks (n = 41) was associated with a significant improvement ($P < .01$) in HRQoL across all preselected scales (Figure 5).[19] The benefit associated with RBC-TI ≥ 8 weeks exceeded the prespecified score difference of ≥ 10 points versus baseline for clinically meaningful improvement in all 5 scales.

In another post hoc analysis, changes in HRQoL from baseline for the 5 preselected scales were not significantly different between lenalidomide nonresponders (ie, lenalidomide-treated patients who did not achieve RBC-TI ≥ 8 weeks) and placebo patients, suggesting that lenalidomide treatment even in the absence of a response had no significant negative effect on HRQoL. However, lenalidomide responders (ie, those who achieved RBC-TI ≥ 8 weeks) did show improvements in all 5 scales compared with lenalidomide nonresponders or placebo patients. This suggests that patients who responded to lenalidomide therapy not only benefitted in terms of becoming RBC-TI, but also experienced a significant alleviation of patient-reported symptoms (see Supplemental Figure 2 in the online version). The incidence of common Grade 3/4 adverse events was comparable between RBC-TI ≥ 8 weeks responders and nonresponders (see Supplemental Table 2 in the online version).

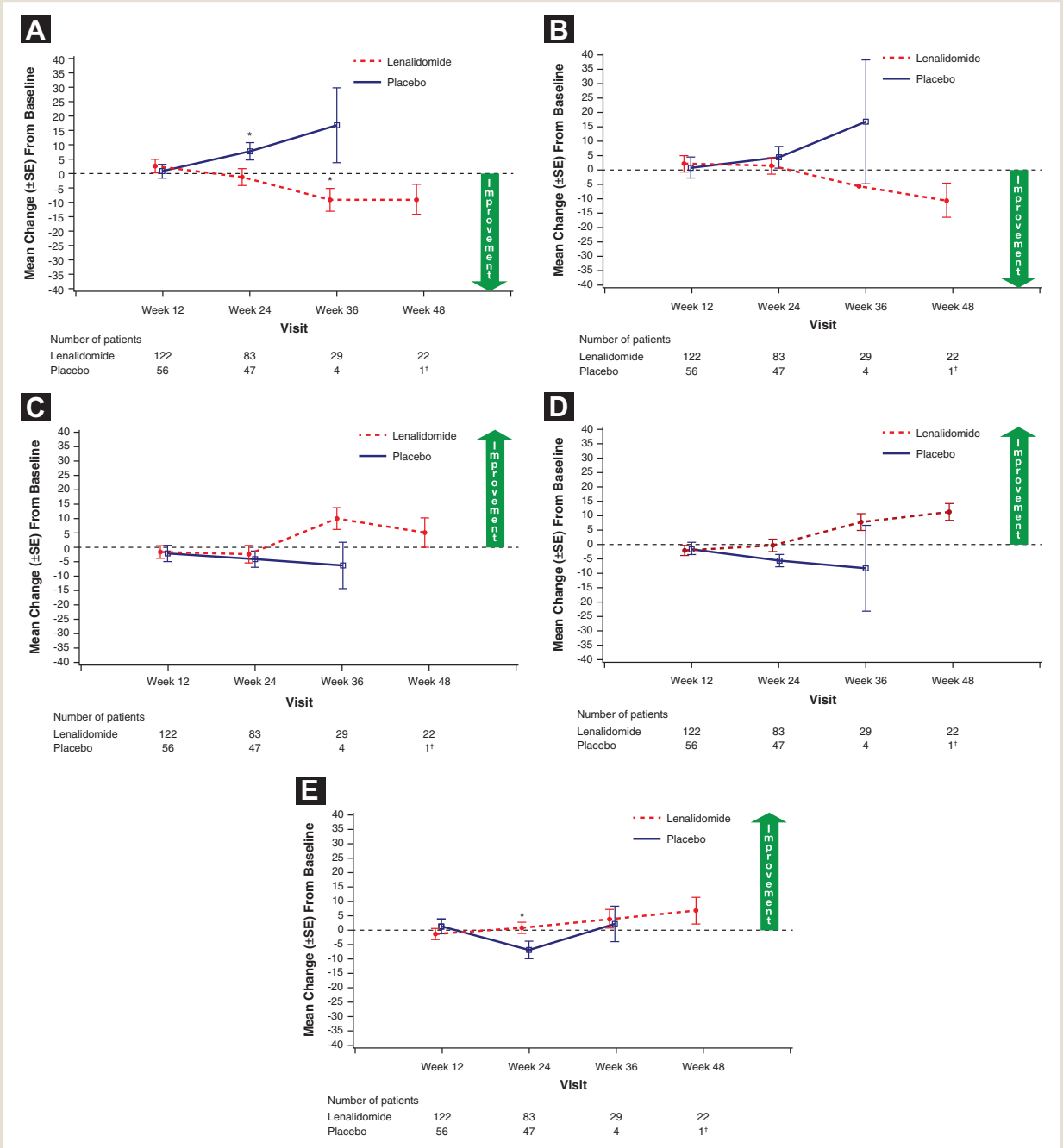
Relationship Between Change in Hemoglobin Level and Changes in HRQoL Outcomes

In a post hoc analysis of the lenalidomide and placebo groups combined, change in hemoglobin level from baseline correlated significantly ($P < .05$) with changes in HRQoL across all scales and time points, except for emotional functioning at weeks 12 and 24 and dyspnea at week 12 (Table 2). Hemoglobin level correlated positively with functional scales and negatively with symptom scales. The strength of the correlation increased from week 12 to week 24.

Discussion

This study provides the first detailed analysis of HRQoL from a randomized, placebo-controlled phase III study of lenalidomide in

Figure 1 Mean Change From Baseline in HRQoL Scores Without Adjusting for Baseline Scores for Preselected EORTC QLQ-C30 Scales: (A) Fatigue, (B) Dyspnea, (C) Global Quality of Life, (D) Physical Functioning, and (E) Emotional Functioning, According to Randomized Treatment Group. * Significant Difference ($P < .05$) Between Treatment Groups. †Data for Placebo Group at Week 48 Not Shown Because of Low Patient Number

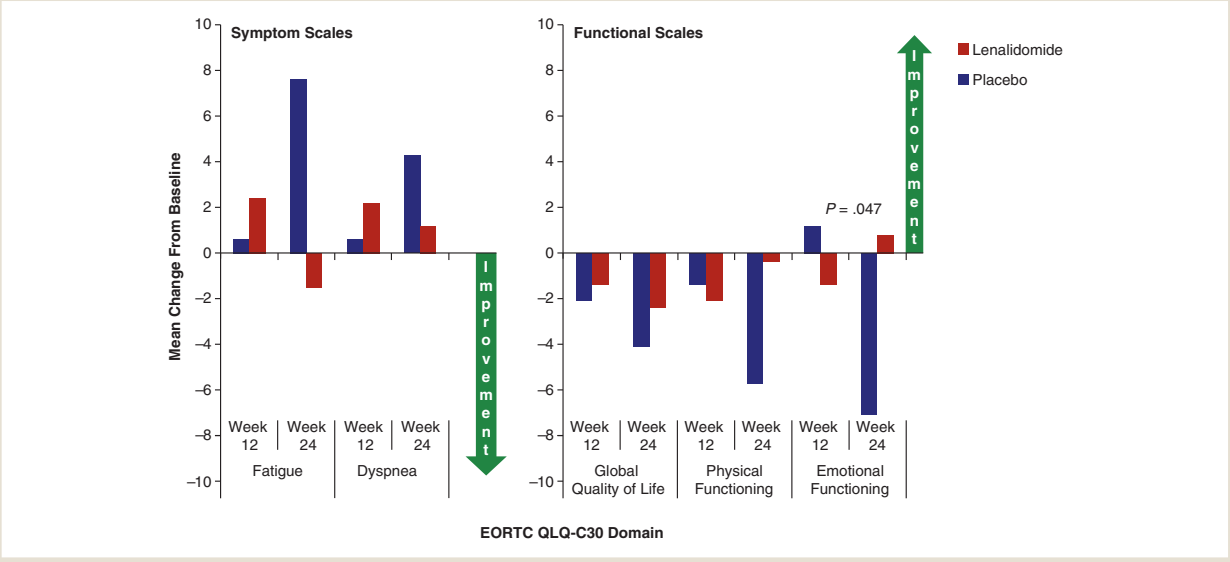


Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life; SE = standard error.

RBC transfusion-dependent patients with lower-risk, non-del(5q) MDS who were ineligible for or refractory to ESAs. Overall, treatment with lenalidomide did not worsen HRQoL compared with placebo, and clinically meaningful improvements were observed at week 24 in a proportion of patients, with a trend toward sustained improvements when lenalidomide treatment was extended beyond 24 weeks. Notably, response to lenalidomide was associated with significant improvements in HRQoL.

Anemia is the most common cause of symptoms in patients with lower-risk MDS,[1] and anemia-related fatigue can negatively affect HRQoL.[27,28] Dependence on RBC transfusions is also associated with worse HRQoL[8,9] and significantly shorter survival.[4,5] In

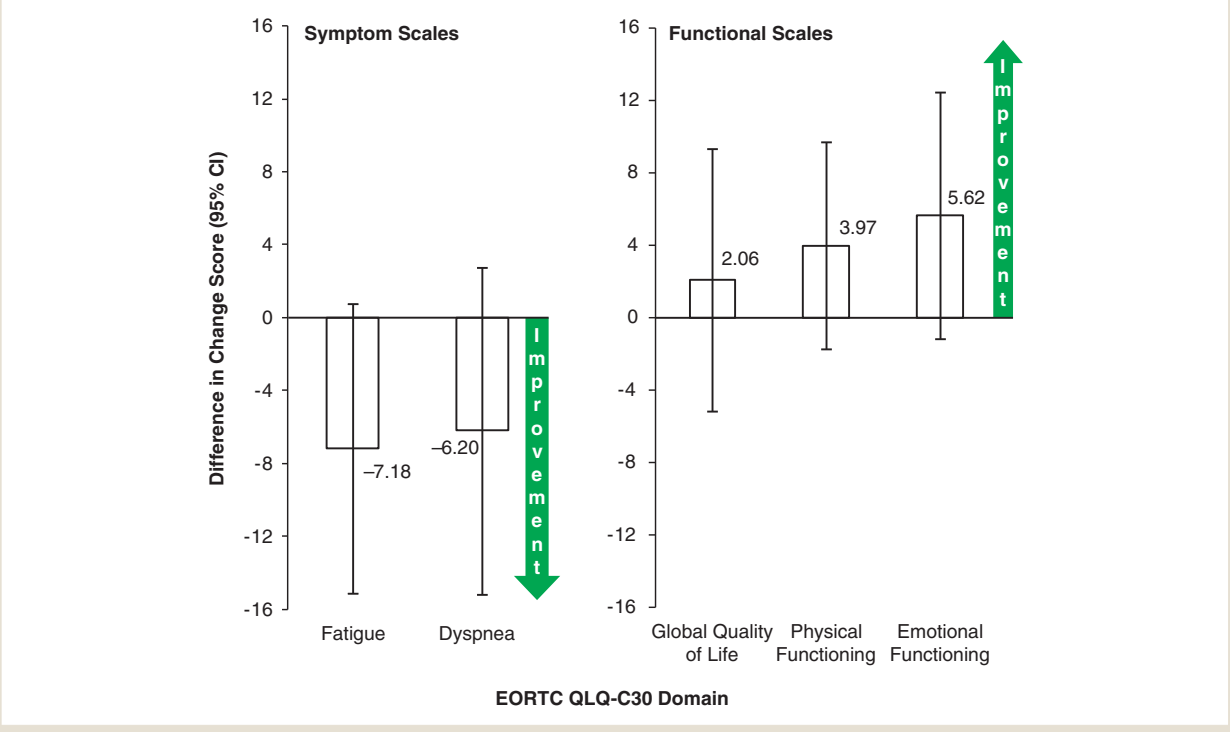
Figure 2 Mean Change From Baseline in HRQoL Scores After Adjusting for Baseline Scores for Preselected EORTC QLQ-C30 Scales According to Randomized Treatment Group



Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life.

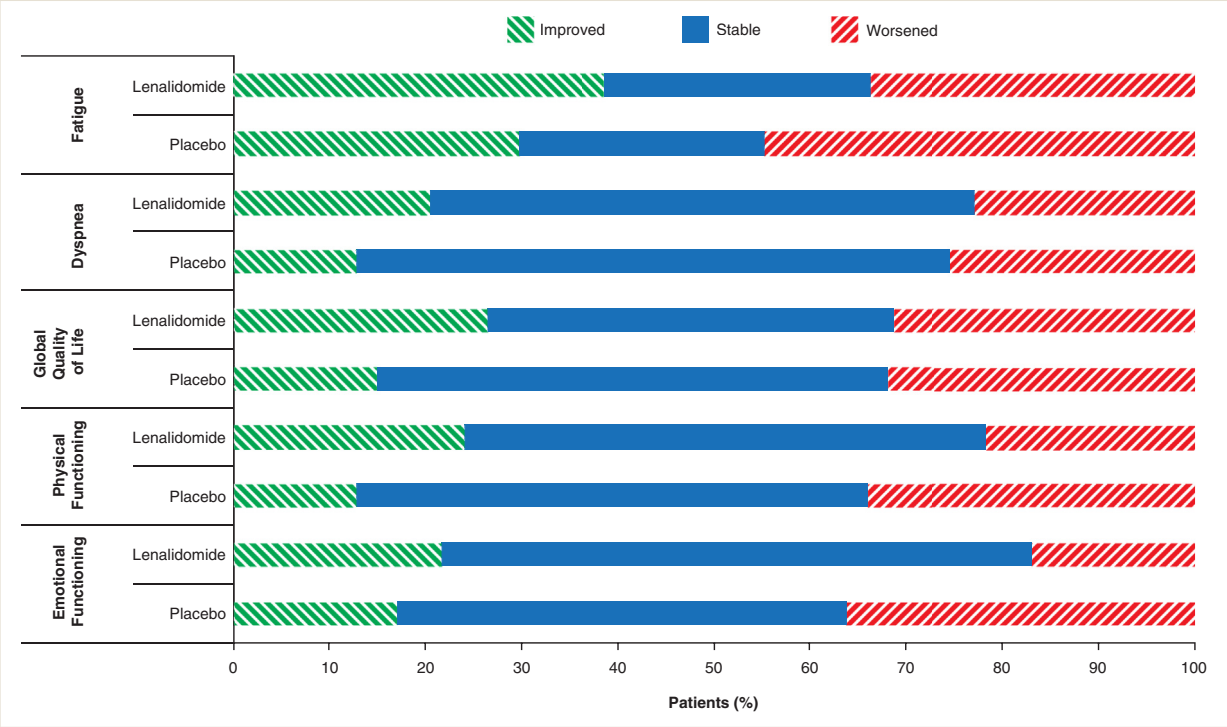
addition, self-reported fatigue severity strongly correlates with patient-perceived symptom severity[29] and might provide prognostic information for overall survival independent of standard risk assessment in patients with higher-risk MDS.[30] Achievement of RBC-TI during lenalidomide therapy was associated with significant improvements in HRQoL. Our findings showed that an increase in

Figure 3 Difference in Predicted Least-Squares Mean Changes for Preselected EORTC QLQ-C30 HRQoL Scales Between Lenalidomide Versus Placebo at Week 24. The Model Included the Following Covariates: Treatment Group, Time (in Weeks), Baseline Score, and a Treatment Group × Time Interaction Term, With Intercept and Time as Random Effects



Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life.

Figure 4 Proportion of Patients With Clinically Meaningful Improvement or Worsening in Scores for Preselected EORTC QLQ-C30 HRQoL Scales at Week 24. A Clinically Meaningful Change Was Defined as a Change of ≥ 10 Points From Baseline



Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life.

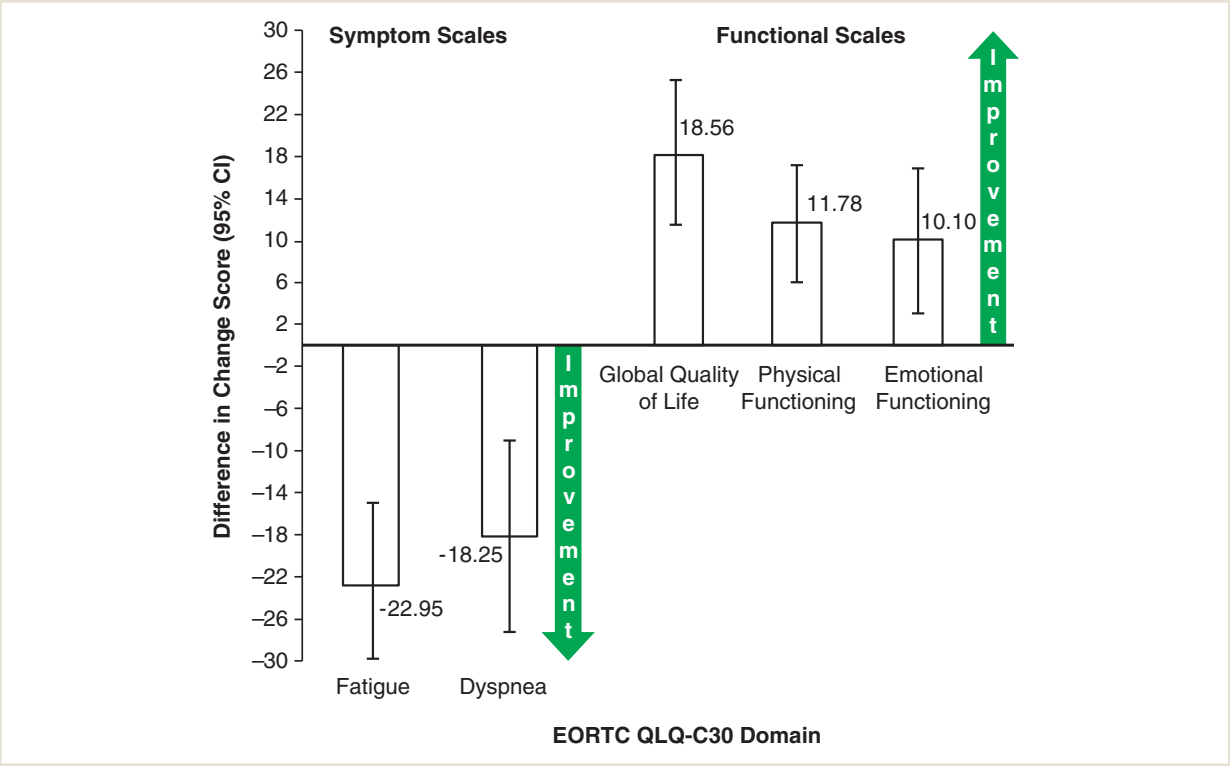
hemoglobin level positively affected HRQoL, and the effect appeared to increase over time. These observations are consistent with previous reports on the effect of hemoglobin level and RBC transfusion dependence on HRQoL in MDS.[8,9,31]

Other studies of lenalidomide in lower-risk MDS have also reported positive effects on HRQoL.[13,14,32] In a phase III study of lower-risk MDS patients with del(5q), scores for the Functional Assessment of Cancer Therapy—Anemia scale improved significantly from baseline in patients treated with lenalidomide 5 mg and 10 mg (+ 5.7 and + 5.7, respectively) versus placebo (− 2.8; both $P < .05$).[13] Improvements were significantly greater in patients who achieved transfusion independence. The HRQoL benefit was apparent after 12 weeks in this patient population with del(5q) MDS. Continued treatment with lenalidomide was associated with further benefits. Similarly, a single-arm phase II trial of patients with anemia and lower-risk del(5q) MDS reported that erythroid response with lenalidomide was associated with significant improvements in several scales of the MDS-specific QOL-E questionnaire compared with nonresponders.[32] Recent findings further suggest that transfusion-independent patients with lower-risk del(5q) MDS and moderate levels of anemia might also benefit from early treatment with lenalidomide in terms of better physical functioning.[14] Our study has found that the HRQoL benefits of lenalidomide in lower-risk MDS are not just restricted to patients with the del(5q) karyotype.

The observed improvements in HRQoL are consistent with the known biological and clinical effects of lenalidomide in lower-risk MDS.[11,12,19,33-35] In a phase II study of transfusion-dependent patients with del(5q), 67% of patients treated with lenalidomide achieved RBC-TI ≥ 8 weeks, with a median peak increase in hemoglobin level of 5.4 g/dL.[11] In a subsequent phase III study, significantly more patients treated with lenalidomide 5 mg and 10 mg achieved RBC-TI ≥ 26 weeks compared with placebo (42.6% and 56.1%, respectively, vs. 5.9%; both $P < .001$).[12] In the MDS-005 phase III study of non-del(5q) lower-risk patients, lenalidomide resulted in RBC-TI ≥ 8 weeks in 26.9% of patients,[19] which was consistent with the response rate observed in the initial phase II MDS-002 trial.[33] Myelosuppression is a common adverse event observed in patients treated with lenalidomide: in MDS-005, the incidence of Grade 3/4 neutropenia and thrombocytopenia was 62% and 36%, respectively.[19] The incidence of common Grade 3/4 adverse events was comparable between responders and nonresponders. In contrast to previous findings in patients with del(5q) from the MDS-003 study,[36] lenalidomide-induced myelosuppression occurring early during treatment did not predict response to lenalidomide in patients with non-del(5q) MDS in the present study (data not shown). In our analysis, achievement of RBC-TI ≥ 8 weeks was nevertheless associated with improved HRQoL. This suggests that, overall, in terms of HRQoL, the positive effects of achieving transfusion independence might outweigh the negative effects of adverse events associated with treatment.

Whereas improvements in HRQoL were observed after 12 weeks of lenalidomide treatment in patients with del(5q),[13] our analysis of

Figure 5 Relationship Between Achievement of RBC-TI ≥ 8 Weeks and Change in HRQoL. For Each EORTC QLQ-C30 Scale, the Effect of RBC-TI ≥ 8 Weeks Achievement on HRQoL Was Adjusted for Other Relevant Covariates, Including Baseline Score, Time (Visits), and Treatment Group



Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life; RBC-TI = red blood cell transfusion independence.

Reproduced with permission from Santini et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol 2016; 34:2988-96.[19]

a non-del(5q) population showed that the HRQoL benefit was delayed until week 24 of treatment. This observation is consistent with the longer median time to onset of RBC-TI in non-del(5q) patients compared with del(5q) patients.[12,19] The reported HRQoL benefits we observed, together with the possibility of selecting patients more likely to respond to lenalidomide based on endogenous erythropoietin level,[19] is encouraging in this ESA-refractory or -ineligible group with otherwise very limited treatment options. Furthermore, the combination of lenalidomide and erythropoietin[37] has been added to the updated National Comprehensive Cancer Network guidelines as a treatment option for patients with lower-risk non-del(5q) MDS who fail to respond or stop responding to ESAs.[38]

A potential limitation of the current study is that only patients who achieved RBC-TI ≥ 8 weeks or erythroid response were allowed to continue treatment after week 24. The small number of patients in this group precludes comparisons of HRQoL between treatment groups beyond week 24. However, the available data after week 24 (in responding patients) suggest continued positive effects of long-term treatment with lenalidomide in terms of HRQoL. Questionnaire-based studies are subject to selection bias due to study dropout and patient-related factors, such as older age and higher level of comorbidity.[39] However, despite the

Table 2 Relationship Between Change From Baseline in Hemoglobin Level and Changes in HRQoL Outcomes for the Combined Lenalidomide and Placebo Groups in Patients With Available Hemoglobin and HRQoL Data at Weeks 12 and 24

Scale of EORTC QLQ-C30	Scheduled Visit	n	Correlation Coefficient	*P*
Symptom Scales				
Fatigue	Week 12	131	−0.24042	.0057
	Week 24	92	−0.45423	<.0001
Dyspnea	Week 12	131	−0.13084	.1363
	Week 24	92	−0.21807	.0368
Functional Scales				
Global quality of life	Week 12	131	0.21277	.0147
	Week 24	92	0.32566	.0015
Physical functioning	Week 12	131	0.19409	.0263
	Week 24	92	0.55735	<.0001
Emotional functioning	Week 12	131	0.09999	.2558
	Week 24	92	0.20479	.0502

Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life.

elderly patient population and electronic method of data collection, compliance rates in this study were high and similar between treatment groups at all assessment visits. Baseline characteristics of compliant and noncompliant patients were comparable, suggesting that the data are representative of all patients in the MDS-005 study and the results are unlikely to be affected by dropouts. Notably, imputation using different methods and missing data assumptions produced consistent results, indicating that bias due to missing data is unlikely. Our results add to the existing evidence showing the utility of the QLQ-C30 in patients with MDS.[29,40,41]

Conclusion

Treatment with lenalidomide did not worsen HRQoL overall compared with placebo in patients with lower-risk non-del(5q) MDS, regardless of responder status. Achievement of RBC-TI $\geq$ 8 weeks during lenalidomide therapy was associated with significant improvements in HRQoL. Continued lenalidomide treatment appeared to maintain or increase improvements in HRQoL. Based on these findings and the results of the MDS-005 trial, lenalidomide represents a treatment option for patients with lower-risk non-del(5q) MDS who are ineligible for or refractory to ESAs, and optimal benefit may be attained when treatment is maintained after achievement of RBC-TI.

Clinical Practice Points

- Transfusion-dependent MDS is associated with poor HRQoL due to anemia-related fatigue and the burden of undergoing chronic transfusions.
- In the MDS-005 phase III study of patients with non-del(5q) lower-risk MDS, 26.9% of patients achieved RBC-TI $\geq$ 8 weeks with lenalidomide treatment. Until this analysis, however, the effect of lenalidomide on patient HRQoL in this setting was relatively unclear.
- Our study shows that HRQoL did not worsen during lenalidomide treatment, and patients who responded to lenalidomide reported significant improvements in HRQoL. Continued lenalidomide treatment appeared to maintain or increase improvements in HRQoL.
- First, these findings highlight the importance of achieving RBC-TI in patients with lower-risk MDS, as this was associated with a significant improvement in patient HRQoL. Achievement of transfusion independence should therefore remain an important goal of therapy for these patients.
- Second, our findings further support the use of lenalidomide in patients with lower-risk non-del(5q) MDS who are refractory to ESAs. Because of the limited treatment options currently available for these patients, the use of lenalidomide in selected patients might help improve patient outcomes, including HRQoL.

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Disclosure

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Supplemental Data

Supplemental figures, tables, and appendix accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2017.12.004.

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Supplemental Appendix A

Additional Methods: Statistical Analyses

The proportion of patients completing the EORTC QLQ-C30 was calculated at each assessment visit. A patient was considered compliant at a particular visit if ≥ 15 of 30 questionnaire items were completed. The denominator for each visit was calculated on the basis of the number of patients who were still receiving the study drug at that time point. The 2-sided Fisher exact test was used to compare the proportion of compliant patients at each assessment visit between treatment groups. Key baseline characteristics between compliant and noncompliant patients were compared between treatment groups using the 2-sided Fisher exact test for categorical variables and the 2-sample *t* test for continuous variables.

For each scale of the QLQ-C30, descriptive statistics of observed scores and change from baseline scores were calculated for each visit. A pooled, 2-sample, 2-sided *t* test was used to determine differences in mean changes from baseline between treatment groups. Between-group comparisons were limited to weeks 12 and 24 because of low patient numbers after 24 weeks. To account for differences in baseline scores between treatment groups, analysis of variance was also performed on change from baseline scores in preselected HRQoL scales between treatment groups. Sensitivity analyses using last observation carried forward, complete-case analysis, and pattern mixture model were performed to assess the effect of missing data on the primary analyses.

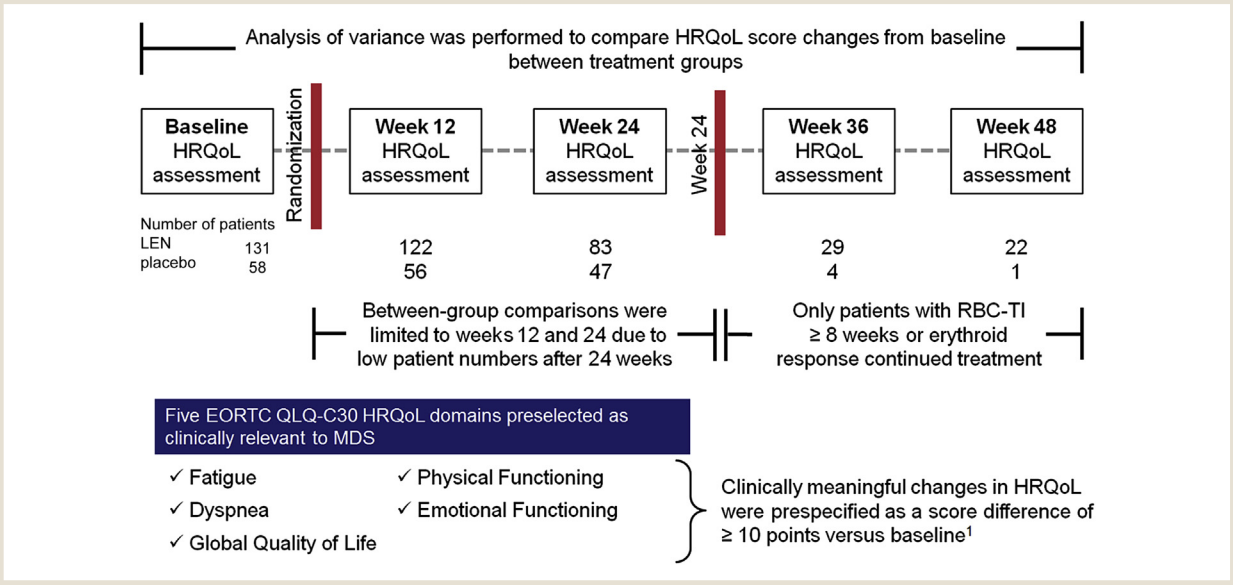
To estimate the effect of treatment on each scale of the QLQ-C30 over time and assess differences between treatment groups, a linear mixed effects repeated measures analysis model with random intercept/slope was used, using a restricted maximum likelihood estimation method. The following covariates were included: treatment group, time (in weeks), baseline score, and a Treatment group × Time interaction term, with intercept and time as random effects. Results were summarized using the least squares means for change from baseline to week 24 within each treatment group and the difference in least squares means between treatment groups.

Clinically meaningful changes in HRQoL scale scores were prespecified as a score difference of ≥ 10 points versus baseline.[1] Patients were accordingly grouped into categories of improvement, no change, or worsening. The 2-sided Fisher exact test was used to compare the proportions of patients within these categories at each postbaseline visit between treatment groups.

A post hoc analysis was performed to assess the effect of RBC-TI, as a time-varying covariate while controlling for other significant factors, on preselected HRQoL scales using a linear mixed-effects regression model to estimate the difference in scores between RBC-TI ≥ 8 weeks responders and nonresponders. The incidence of Grade 3/4 adverse events was analyzed according to RBC-TI ≥ 8 weeks response in lenalidomide-treated patients. Adverse events were coded as in the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). In addition, a post hoc analysis was conducted to assess the relationship between change in hemoglobin level and changes in HRQoL outcomes at weeks 12 and 24 across all 5 preselected scales. The postbaseline hemoglobin collection dates were matched with the HRQoL assessments to obtain hemoglobin data on the same day as the HRQoL visit. The association between variables was analyzed using the Pearson correlation coefficient.

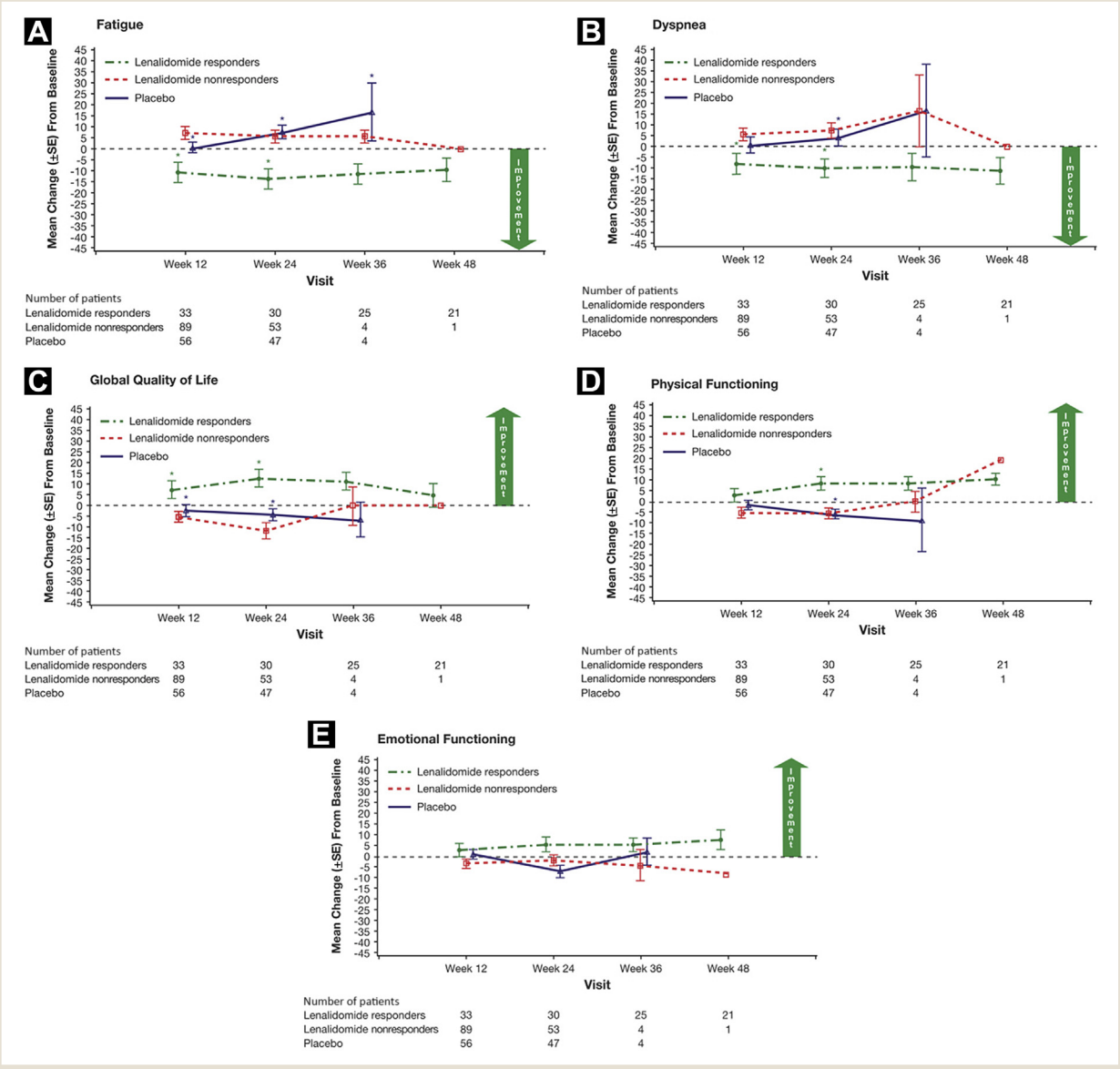
The data cutoff date for inclusion in this analysis was March 17, 2014.

Supplemental Figure 1 Assessment of HRQoL in the MDS-005 Study



Abbreviations: HRQoL = health-related quality of life; LEN = lenalidomide; MDS = myelodysplastic syndromes; RBC-TI = red blood cell transfusion independence.

Supplemental Figure 2 Mean Change From Baseline in HRQoL Scores Without Adjusting for Baseline Scores for Preselected EORTC QLQ-C30 Scales (A: Fatigue, B: Dyspnea, C: Global Quality of Life, D: Physical Functioning, E: Emotional Functioning) in Lenalidomide Responders, Lenalidomide Nonresponders, and Placebo Patients. *$P < .05$ for the Comparison of Lenalidomide Responders Versus Lenalidomide Nonresponders; Lenalidomide Nonresponders Versus Placebo; Lenalidomide Responders Versus Placebo



Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life; SE = standard error.

Supplemental Table 1 Mean Scores of EORTC QLQ-C30 Scales at Baseline Among HRQoL-Evaluable Patients From the MDS-005 Study (Lenalidomide and Placebo Columns) and the General Population[2]

EORTC QLQ-C30 Scale	Lenalidomide (n = 131)	Placebo (n = 58)	General Population (n = 7802)
Global Quality of Life	57.1 (21.96)	59.9 (17.27)	71.2 (22.4)
Physical Functioning	69.6 (20.95)	73.1 (17.35)	89.8 (16.2)
Role Functioning	68.8 (30.48)	74.7 (25.02)	84.7 (25.4)
Emotional Functioning	76.8 (21.27)	78.7 (20.72)	76.3 (22.8)
Cognitive Functioning	83.5 (19.99)	88.2 (14.65)	86.1 (20.0)
Social Functioning	80.0 (23.79)	82.5 (21.04)	87.5 (22.9)
Fatigue	42.8 (26.23)	37.5 (20.37)	24.1 (24.0)
Nausea/Vomiting	4.1 (10.36)	5.7 (12.70)	3.7 (11.7)
Pain	21.9 (29.89)	21.3 (26.27)	20.9 (27.6)
Dyspnea	30.3 (30.51)	31.6 (29.57)	11.8 (22.8)
Insomnia	27.7 (30.7)	27.0 (31.50)	21.8 (29.7)
Appetite Loss	15.5 (27.21)	8.6 (15.99)	6.7 (18.3)
Constipation	17.0 (26.59)	15.5 (23.54)	6.7 (18.4)
Diarrhea	9.7 (21.28)	8.0 (18.00)	7.0 (18.0)
Financial Difficulties	13.2 (25.38)	15.5 (24.36)	9.5 (23.2)

Data are presented as mean score (SD). A clinically meaningful change was defined as a change of $\geq$ 10 points from baseline.
Abbreviations: EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30; HRQoL = health-related quality of life.

Supplemental Table 2 Grade 3/4 TEAEs in Lenalidomide-Treated Patients According to RBC-TI ≥8 Weeks Response

Adverse Event	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Patients With ≥ 1 Grade 3/4 TEAE	39 (90.7)	99 (84.6)	1 (50.0)	34 (44.2)
Blood and Lymphatic System Disorders	37 (86.0)	81 (69.2)	1 (50.0)	16 (20.8)
Neutropenia	35 (81.4)	64 (54.7)	0	9 (11.7)
Thrombocytopenia	15 (34.9)	42 (35.9)	0	3 (3.9)
Leukopenia	10 (23.3)	8 (6.8)	0	1 (1.3)
Anemia	2 (4.7)	7 (6.0)	0	4 (5.2)
Bone marrow reticulin fibrosis	0	1 (0.9)		
Coagulopathy	0	1 (0.9)		
Hemolysis	0	1 (0.9)		
Pancytopenia	0	1 (0.9)		
Febrile neutropenia	1 (2.3)	0	1 (50.0)	0
Lymphopenia	1 (2.3)	0		
Infections and Infestations	4 (9.3)	19 (16.2)	0	3 (3.9)
Pneumonia	3 (7.0)	6 (5.1)	0	2 (2.6)
Neutropenic sepsis	0	3 (2.6)		
Urinary tract infection	0	2 (1.7)	0	1 (1.3)
Atypical pneumonia	0	1 (0.9)		
Bronchitis	0	1 (0.9)		
Bronchopneumonia	0	1 (0.9)		
Cellulitis	0	1 (0.9)		
Escherichia sepsis	0	1 (0.9)		
Folliculitis	0	1 (0.9)		
Parotitis	0	1 (0.9)		
Peritonitis bacterial	0	1 (0.9)		
Pneumonia viral	0	1 (0.9)		
Staphylococcal infection	0	1 (0.9)		
Tooth abscess	0	1 (0.9)		
Lobar pneumonia	1 (2.3)	0		
Influenza			0	1 (1.3)
General Disorders and Administration-Site Conditions	4 (9.3)	11 (9.4)	0	2 (2.6)
Asthenia	1 (2.3)	5 (4.3)	0	1 (1.3)
Fatigue	1 (2.3)	4 (3.4)	0	1 (1.3)
Face edema	0	1 (0.9)		
Edema peripheral	0	1 (0.9)		
General physical health deterioration	1 (2.3)	0		
Malaise	1 (2.3)	0		
Investigations	4 (9.3)	10 (8.5)	0	4 (5.2)
Liver function test abnormal	0	2 (1.7)		
Alanine aminotransferase increased	2 (4.7)	1 (0.9)	0	1 (1.3)
Blood bilirubin increased	0	1 (0.9)		
Blood creatinine increased	0	1 (0.9)		
Blood glucose increased	0	1 (0.9)		
C-reactive protein increased	0	1 (0.9)		
HLA marker study positive	0	1 (0.9)		
Mycobacterium test positive	0	1 (0.9)		
Oxygen saturation decreased	0	1 (0.9)		

Supplemental Table 2 Continued

Adverse Event	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Troponin increased	0	1 (0.9)	0	1 (1.3)
Aspartate aminotransferase increased	1 (2.3)	0		
Weight decreased	1 (1.3)	0	0	1 (1·3)
Gamma-glutamyltransferase increased			0	1 (1.3)
Serum ferritin increased			0	1 (1.3)
Metabolism and Nutrition Disorders	2 (4.7)	10 (8.5)	0	5 (6.5)
Hypokalemia	1 (2.3)	6 (5.1)		
Decreased appetite	0	1 (0.9)		
Hyperglycemia	0	1 (0.9)		
Hyperkalaemia	0	1 (0.9)		
Hypocalcemia	0	1 (0.9)		
Iron overload	1 (2.3)	1 (0.9)	0	2 (2.6)
Fluid overload			0	1 (1.3)
Hyperuricemia			0	1 (1.3)
Hypoglycemia			0	1 (1.3)
Gastrointestinal Disorders	1 (2.3)	8 (6.8)	0	4 (5.2)
Diarrhea	0	4 (3.4)		
Abdominal pain	0	1 (0.9)	0	1 (1.3)
Ascites	0	1 (0.9)		
Gastrointestinal necrosis	0	1 (0.9)		
Hematemesis	0	1 (0.9)		
Nausea	0	1 (0.9)		
Inguinal hernia, obstructive	1 (2.3)	0		
Constipation			0	2 (2.6)
Diverticulum			0	1 (1.3)
Pancreatitis			0	1 (1.3)
Pancreatitis, necrotizing			0	1 (1.3)
Skin and Subcutaneous Tissue Disorders	3 (7.0)	8 (6.8)	0	2 (2.6)
Drug eruption	0	1 (0.9)		
Dry skin	0	1 (0.9)		
Exfoliative rash	0	1 (0.9)		
Neurodermatitis	0	1 (0.9)		
Pruritus	2 (4.7)	1 (0.9)	0	2 (2.6)
Rash erythematous	0	1 (0.9)		
Rash pruritic	0	1 (0.9)		
Skin ulcer	1 (2.3)	1 (0.9)		
Urticaria	0	1 (0.9)		
Rash, other	1 (2.3)	0		
Respiratory, Thoracic, and Mediastinal Disorders	1 (2.3)	7 (6.0)	0	3 (3.9)
Dyspnea	0	3 (2.6)	0	3 (3.9)
Pleural effusion	0	2 (1.7)		
Acute respiratory distress syndrome	0	1 (0.9)		
Epistaxis	0	1 (0.9)		
Hypoxia	0	1 (0.9)		
Lung disorder	0	1 (0.9)		
Asthma	1 (2.3)	0		

Supplemental Table 2 Continued

Adverse Event	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Cardiac Disorders	0	6 (5.1)	0	5 (6.5)
Cardiac failure	0	2 (1.7)	0	1 (1.3)
Myocardial infarction	0	2 (1.7)	0	1 (1.3)
Atrial fibrillation	0	1 (0.9)	0	3 (3.9)
Cardiac failure congestive	0	1 (0.9)		
Atrial flutter			0	1 (1.3)
Ventricular arrhythmia			0	1 (1.3)
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	1 (2.3)	4 (3.4)	0	5 (6.5)
Myelodysplastic syndromes	0	2 (1.7)		
Adenocarcinoma of colon	0	1 (0.9)		
Lung squamous cell carcinoma stage IV	0	1 (0.9)		
Invasive ductal breast carcinoma	1 (2.3)	0		
Acute myeloid leukemia			0	2 (2.6)
Chronic myelomonocytic leukemia			0	1 (1.3)
Prostate cancer			0	1 (1.3)
Squamous cell carcinoma of lung			0	1 (1.3)
Musculoskeletal and Connective Tissue Disorder	0	3 (2.6)	0	1 (1.3)
Intervertebral disc protrusion	0	1 (0.9)		
Osteoarthritis	0	1 (0.9)		
Pain in jaw	0	1 (0.9)		
Rhabdomyolysis			0	1 (1.3)
Nervous System Disorders	0	3 (2.6)		
Headache	0	1 (0.9)		
Lethargy	0	1 (0.9)		
Syncope	0	1 (0.9)		
Vascular Disorders	2 (4.7)	3 (2.6)	0	1 (1.3)
Deep vein thrombosis	1 (2.3)	2 (1.7)		
Circulatory collapse	0	1 (0.9)	0	1 (1.3)
Hypotension	1 (2.3)	0		
Hepatobiliary Disorders	0	2 (1.7)	0	2 (2.6)
Hepatic cirrhosis	0	1 (0.9)	0	1 (1.3)
Hepatic failure	0	1 (0.9)		
Hyperbilirubinemia	0	1 (0.9)	0	1 (1.3)
Jaundice	0	1 (0.9)		
Biliary colic			0	1 (1.3)
Injury, Poisoning, and Procedural Complications	4 (9.3)	2 (1.7)		
Femoral neck fracture	0	1 (0.9)		
Hip fracture	0	1 (0.9)		
Femur fracture	2 (4.7)	0		
Lumbar vertebral fracture	1 (2.3)	0		
Thoracic vertebral fracture	1 (2.3)	0		
Traumatic intracranial hemorrhage	1 (2.3)	0		
Renal and Urinary Disorders	2 (4.7)	2 (1.7)		
Pollakiuria	0	1 (0.9)		
Renal failure acute	0	1 (0.9)		

Supplemental Table 2 Continued

Adverse Event	Lenalidomide		Placebo	
	RBC-TI ≥ 8 Weeks Responders (n = 43)	RBC-TI ≥ 8 Weeks Nonresponders (n = 117)	RBC-TI ≥ 8 Weeks Responders (n = 2)	RBC-TI ≥ 8 Weeks Nonresponders (n = 77)
Nephrolithiasis	1 (2.3)	0		
Renal colic	1 (2.3)	0		
Renal failure chronic	1 (2.3)	0		
Ear and Labyrinth Disorders	0	1 (0.9)		
Middle ear inflammation	0	1 (0.9)		
Psychiatric Disorders	2 (4.7)	0	0	2 (2.6)
Confusional state	1 (2.3)	0	0	1 (1.3)
Insomnia	1 (2.3)	0		
Mental status changes	1 (2.3)	0		
Anxiety			0	1 (1.3)

Data are presented as n (%).
Abbreviations: HLA = human leukocyte antigen; RBC-TI = red blood cell transfusion independence; TEAE = treatment-emergent adverse event.

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